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Complex Mixtures of Urban Air Pollutants Identification and Comparative Assessment of Mutagenic and Tumorigenic Chemicals and Emission Sources

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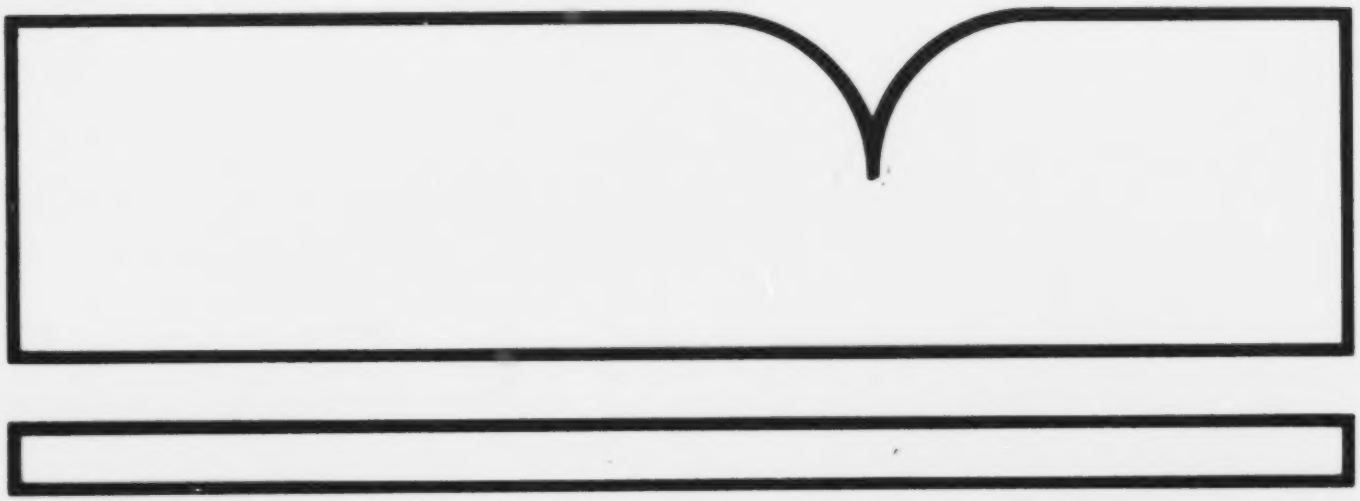

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16. ABSTRACT

Advances in the cancer risk assessment of complex mixtures of urban air pollutants requires the development of new methods to advance our understanding of low dose and inter-species extrapolations in predicting human risk. Current research is focusing on the identification and source apportionment of airborne carcinogens and the development of new exposure, dosimetry and extrapolation methods which can be applied to complex mixture problems. Research on the identification of the genotoxic compounds in urban air and particularly on the polar mutagenic compounds, many of which appear to be nitrated and or oxygenated aromatic compounds, is advancing with the use of micromutagenesis methods coupled to analytical fractionation and new chemical characterization methods. In order to control and reduce human exposure from potentially hazardous emission sources which contribute to urban air pollution, apportionment of the potential genotoxic hazard by source is critical. Source apportionment of the mutagenic activity observed in urban air shows that the small area combustion sources, vehicles and residential heating, are the major contributors to the ambient mutagenicity of the aerosol fraction. The potential hazard and sources of the gaseous emissions has not been determined, however, they appear to be significantly increased by atmospheric transformation by ozone and nitrogen oxides. Comparative mutagenesis, carcinogenesis and DNA adduct dosimetry studies are being conducted to develop new exposure, dosimetry and extrapolation methods for cancer risk assessment of complex urban air pollutants. These studies are being conducted with current environmental combustion emission sources and urban aerosol samples as well as with emission sources for which human lung cancer data and human tissues are available for comparative assessment. The combined application of these methods will provide an alternative approach to cancer risk assessment of complex mixtures of urban air pollutants.

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COMPLEX MIXTURES OF URBAN AIR POLLUTANTS: Identification and Comparative Assessment of Mutagenic and Tumorigenic Chemicals and Emission Sources

Joellen Lewtas and Jane Gallagher

U.S. Environmental Protection Agency
Health Effects Research Laboratory
Genetic Toxicology Division
Genetic Bioassay Branch
Research Triangle Park, NC 27711

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INTRODUCTION

Urban areas are plagued with air pollution from many sources, particularly combustion sources. Although industrialization has often been considered the primary source of urban air pollution, recent studies suggest that vehicles and residential heating sources are more important than previously recognized. Complex mixtures of combustion emissions resulting in urban air pollution have been estimated to contribute as much as 10% of the lung cancer cases based on urban versus rural cancer rates (Holmberg and Ahlborg, 1973). In highly urbanized areas (e.g., large cities) this air pollution risk has been estimated to contribute 5-10 lung cancer cases per 100,000 miles per year. Such risk estimations are recognized as highly uncertain since they were derived without the use of quantitative exposure estimations and are dependent on the estimated contribution of cigarette smoke to the lung cancer rates.

Air pollution consists of a very complex mixture of gases and particles with condensed organic matter. These pollutants are emitted from many sources (e.g., vehicles, industry, power sources) and may undergo chemical and physical changes in the atmosphere. The extractable organic matter (EOM) from air particles was found to be carcinogenic in rodents as early as

the 1940's (Leiter et al., 1942; Hueper et al., 1962) and later short-term bioassays demonstrated that similar organic extracts induced oncogenic transformations in mammalian cells (Freeman et al., 1971; Gordon et al., 1973) and mutations in bacteria (Tokiwa et al., 1976; Pitts et al., 1977). Very few studies have been conducted to directly evaluate the mutagenicity or carcinogenicity of the complex mixture of gases in urban air. Limited studies in the plant, Tradescantia (Schairer et al., 1982), and in bacteria suggest that mixtures of urban gases are also mutagenic (Claxton, 1985). Recent evidence also suggests that atmospheric transformation reactions can dramatically increase the mutagenic activity of complex mixtures of gaseous organics from wood combustion (Kleindienst et al., 1986).

Current research on the EOM from urban air particles is focused on the objectives of identifying the principal emission sources and chemicals contributing to potential cancer risk from the particles. Two strategies or approaches for accomplishing these objectives which are addressed here are: 1) bioassay-directed fractionation and chemical characterization for the identification of genotoxic agents and 2) source apportionment of airborne mutagens and estimation of the comparative cancer risk from the major sources of mutagens. Source apportionment is a combination of

mathematical and analytical procedures, which are used to determine the contribution of specific emission sources to ambient concentrations of air pollution. Short-term genetic bioassays have been coupled with sampling and analysis procedures to allow identification and source apportionment of mutagens. Comparative mutagenicity, tumorigenicity and DNA adduct dosimetry studies will provide new data for cancer risk assessment of complex mixtures of urban air pollution.

IDENTIFICATION OF AIRBORNE MUTAGENS AND CARCINOGENS

Bioassay-directed fractionation and chemical characterization has been successfully used to identify mutagens in both combustion sources (e.g., diesel emissions) and ambient air particles (Schuetzle and Lewtas, 1986). The *Salmonella typhimurium* histidine reversion assay has been the most widely used assay for detection of mutagens. Studies of the organics associated with air particles have demonstrated that more mutagenicity is associated with both the organic acids and polar neutral organics than the unsubstituted polycyclic aromatic hydrocarbons (PAH) (Alfheim et al, 1983; Nishioka et al., 1985).

Recent development of micromutagenesis methods coupled to high pressure liquid chromatographic (HPLC) separation

techniques (Lewtas, 1988) have led to the identification of hydroxylated nitro-PAH and hydroxylated nitro polycyclic aromatic ketones in highly mutagenic polar fractions of EOM from air particles (Nishioka et al., 1988). The organic acids contained relatively high concentrations of hydroxylated nitroaromatic compounds where the aromatic portion consisted of one- and two-rings (e.g., hydroxylated nitrobenzene, -toluene, -naphthalene, and -biphenyl isomers). The presence of hydroxylated nitro-PAH have been suggested by Nielsen et al. (1983) and Schuetzle (1983) to account for the mutagenicity in EOM more polar than the PAH and nitro-PAH presumably arising from atmospheric hydroxylation of PAH followed by ortho and para nitration (Pitts, 1983). Zielinska et al. (1986) have demonstrated the formation of hydroxylated nitro-fluoranthene in controlled atmospheric chamber studies, however, the use of bioassay-directed fractionation has greatly facilitated our recent detection of these compounds in ambient air (Nishioka et al., 1988).

SOURCE APPORTIONMENT OF AIRBORNE MUTAGENS

To decrease human exposure to mutagens and carcinogens, the major sources of carcinogenic compounds or their precursors need to be identified. Source apportionment of

urban aerosol (particle) concentrations has been estimated using dispersion modeling, receptor modeling or some combination of these methods (Gordon, 1988). Dispersion models rely on the use of emission factors for each source as the input data to a simple box model or more sophisticated meteorologically based model (e.g., plume model) to predict ambient concentrations of pollutants. Receptor models are generally based on the assumption that tracer species emitted by sources are transported to the receptor (ambient location) in the same way as the source's total emissions so that measurements made at the receptor site are a linear sum of the individual source contributions. Receptor models generally use one of the following methods: chemical mass balance, factor analysis, or multiple linear regression analysis (Gordon, 1988). We have applied these methods both indirectly and directly to the source apportionment of airborne mutagens. Initially either mutagenic emission factors (revertants/kg fuel consumption) or mutagenic potency values (rev/μg EOM or rev/mg particle) were applied to previously reported studies which apportioned the particles in urban air (Lewtas et al., unpublished). The dispersion modeling results show the same major sources of mutagens as the receptor modeling, Fig. 1. These studies suggested that area sources such as vehicles and residential heating account for most of the mutagenicity found

in the urban aerosol (particle phase). Major industrial and utility (e.g., power) sources had little impact. None of these models take into account potential alterations in the ambient mutagenicity resulting from atmospheric transformation. We anticipate that the uncertainty introduced by atmospheric transformation using these relatively simple apportionment methods would be smaller for the airborne particles than for the gases. Recent studies conducted as a part of the U.S. EPA's Integrated Air Cancer Project have monitored ambient mutagenicity for direct use in a multiple linear regression model to apportion the ambient mutagenicity. These studies conducted in relatively simple urban airsheds in Albuquerque, NM (Fig. 2) and Raleigh, NC showed that woodsmoke from residential heating and vehicular emissions were the principal sources of mutagens in the winter in these airsheds (Lewis et al., 1988; Stevens et al., in press).

APPORTIONMENT AND ESTIMATION OF THE CANCER RISK

Research to develop a comparative potency method to determine the potential cancer risk from combustion emission particles was initiated by EPA as part of our diesel research program (Lewtas et al., 1981; Albert et al., 1983). This method utilizes comparative dose-response studies in short-

term mutagenesis bioassays and mouse skin tumor initiation data combined with a comparative analysis using human epidemiological data on similar or related emissions to estimate the cancer risk for a combustion source for which there is no human data (Albert et al., 1983; Lewtas, 1985a, b, 1988; Nesnow, 1988). Application of tumor initiation dose-response data to the source apportionment of EOM and mutagens in Albuquerque, NM results (Fig. 2) shows that the relative contribution of woodsmoke and vehicles to the tumorigenicity is very similar to these source contributions to the mutagenicity. Application of this methodology to apportionment of cancer risk in urban air using unit risk values from the comparative potency method (Lewtas, 1988) also results in a very similar distribution of source contribution to the potential cancer risks. These studies all show that particle emissions from vehicles and residential heating make a major contribution to the potential cancer risk of urban aerosols.

DNA ADDUCT DOSIMETRY OF COMPLEX URBAN AEROSOLS

Assessment of the exposure and biologically effective dose of complex mixtures has presented serious methodological problems. These problems were primarily associated with the

selection of surrogate chemical(s) for exposure and dosimetry studies. The development of a ^{32}P-postlabeling method to detect low levels of DNA adducts (Randerath et al., 1985) arising from unknown constituents of complex mixtures provides a new approach to this problem which is not dependent on preselecting surrogate chemicals. We are further developing and applying these new methodologies to assess the relationships between exposure, DNA adduct formation, mutagenicity, and mouse skin tumor initiating activity for EOM from complex mixtures of urban air particles compared to specific combustion emission sources.

Urban air particles from a winter airshed containing vehicle emissions and woodsmoke are being evaluated for comparative mutagenicity and tumor initiating activity (Lewtas, in press). Dose-response skin tumor initiation studies on the EOM are being conducted in Sencar mice simultaneously with studies to detect and quantitate DNA adduct in multiple tissues. A diagonal zone of radioactivity resulting from the formation of multiple DNA adducts was observed both in bacterial DNA, mouse skin, and lung DNA after exposure to the urban air and other complex mixtures of combustion and related emissions. These results are consistent with the bioassay-directed fractionation studies demonstrating the presence of many genotoxic compounds and

isomers in several chemical fractions. The relative adduct levels for DNA adducts measured 24h after treatment with EOM from urban air particles, coke oven mains and diesel particles is shown in Fig. 3. The urban aerosol extract resulted in a level of DNA adducts in the mouse skin (site of application) and lung DNA that was comparable to that for the diesel treatment, but significantly lower than the adduct level observed for the coke oven treatment. DNA adducts for all these emissions and the urban air extracts were measured in a chromatographic region where a major benzo(a)pyrene (BaP) derived adduct was detected (Gallagher et al., unpublished). The concentration of BaP in these mixtures does not account for the much higher adduct level found in the BaP adduct zone. Future research will be aimed at resolving and identifying the nature of these adducts and their sources.

SUMMARY

Advances in the cancer risk assessment of complex mixtures of urban air pollutants requires the development of new methods to advance our understanding of low dose and inter-species extrapolations in predicting human risk. Current research is focusing on the identification and source apportionment of airborne carcinogens and the development of

new exposure, dosimetry and extrapolation methods which can be applied to complex mixture problems.

Research on the identification of the genotoxic compounds in urban air and particularly on the polar mutagenic compounds, many of which appear to be nitrated and or oxygenated aromatic compounds, is advancing with the use of micromutagenesis methods coupled to analytical fractionation and new chemical characterization methods. In order to control and reduce human exposure from potentially hazardous emission sources which contribute to urban air pollution, apportionment of the potential genotoxic hazard by source is critical. Source apportionment of the mutagenic activity observed in urban air shows that the small area combustion sources, vehicles and residential heating, are the major contributors to the ambient mutagenicity of the aerosol fraction. The potential hazard and sources of the gaseous emissions has not been determined, however, they appear to be significantly increased by atmospheric transformation by ozone and nitrogen oxides.

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FIGURE LEGENDS

Figure 1. Source Apportionment of Airborne Mutagenicity. Mutagenic emission factors were used in a dispersion model for a model Scandanavian town of 100,000 at two sites: Site A where vehicle exhaust dominated and Site B where residential heating dominated (Alfheim et al., 1986). Mutagenic potency values were applied to a source apportionment of the organic carbon in Denver, Colorado using receptor modeling. All three cases shown are for winter.

Figure 2. Receptor Modeling of the Mutagenic and Tumor Initiating Activity in Urban Air Particle Extracts from Albuquerque NM. Mutagenic activity

measurements were directly used in a multilinear regression receptor model (Lewis et al., 1988). Tumor initiating activity for woodsmoke and motor vehicles (Lewtas, 1988) was applied to the source apportionment of the EOM from the Albuquerque air particles.

Figure 3. DNA Adduct Formation in Mouse Skin and Lung Tissue Following Skin Application of Complex Mixtures of Urban Air and Other Combustion and Related Emissions. Representative histogram of the relative adduct levels of skin and lung DNA following skin application of 20 mg of each extract per mouse. Relative adduct labeling (RAL) concentrations are determined as follows: counts per min. (CPM) adducts in the diagonal radioactive zone (DRZ)/cpm in normal nucleotides x 10^8. The y axis shows RAL per mg extract applied per g of mouse body weight. Data represent the mean ± SD from 2-3 determinations from at least two separate ^{32}P-postlabeling analyses. This summary table combines data from two studies using C-57 and Sencar mice.

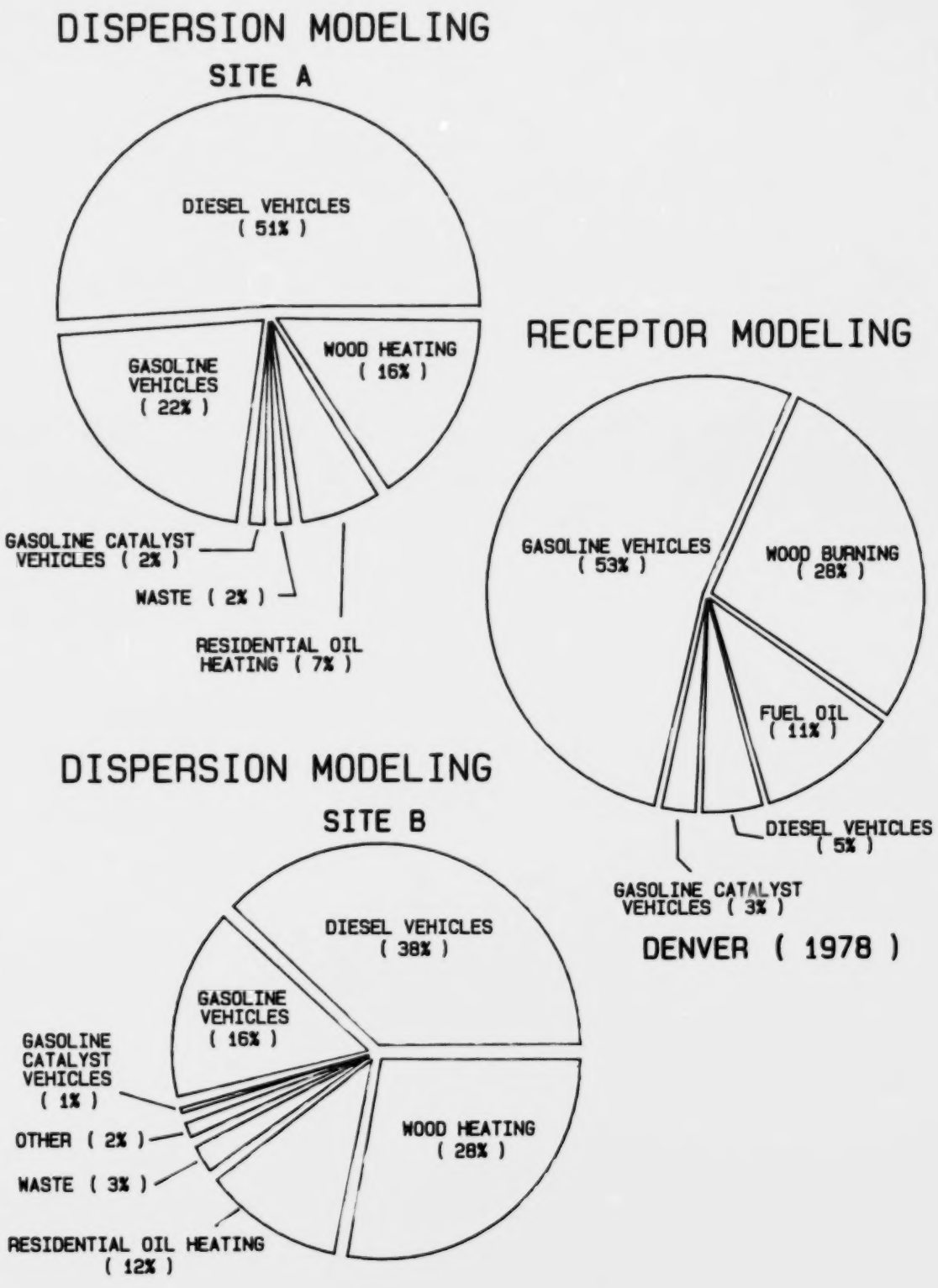
DISPERSION MODELING
SITE A
DIESEL VEHICLES (51%)
GASOLINE VEHICLES (22%)
WOOD HEATING (16%)
GASOLINE CATALYST VEHICLES (2%)
WASTE (2%)
RESIDENTIAL OIL HEATING (7%)
RECEPTOR MODELING
GASOLINE VEHICLES (53%)
WOOD BURNING (28%)
FUEL OIL (11%)
DIESEL VEHICLES (5%)
GASOLINE CATALYST VEHICLES (3%)
DENVER (1978)
DISPERSION MODELING
SITE B
DIESEL VEHICLES (38%)
GASOLINE VEHICLES (16%)
GASOLINE CATALYST VEHICLES (1%)
OTHER (2%)
WASTE (3%)
RESIDENTIAL OIL HEATING (12%)
WOOD HEATING (28%)

Figure 1.

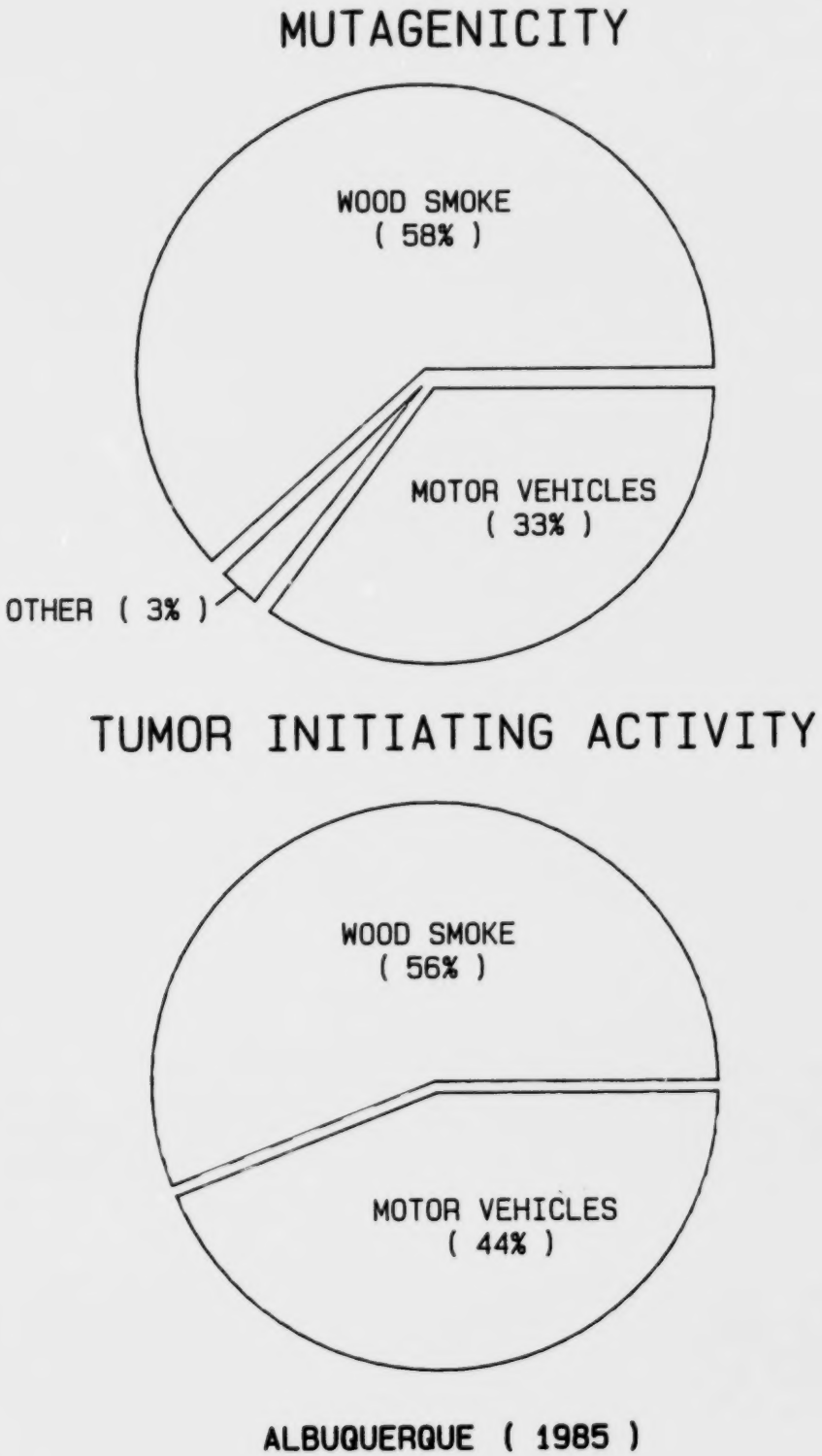
MUTAGENICITY
WOOD SMOKE
(58%)
MOTOR VEHICLES
(33%)
OTHER (3%)
TUMOR INITIATING ACTIVITY
WOOD SMOKE
(56%)
MOTOR VEHICLES
(44%)
ALBUQUERQUE (1985)

Figure 2.

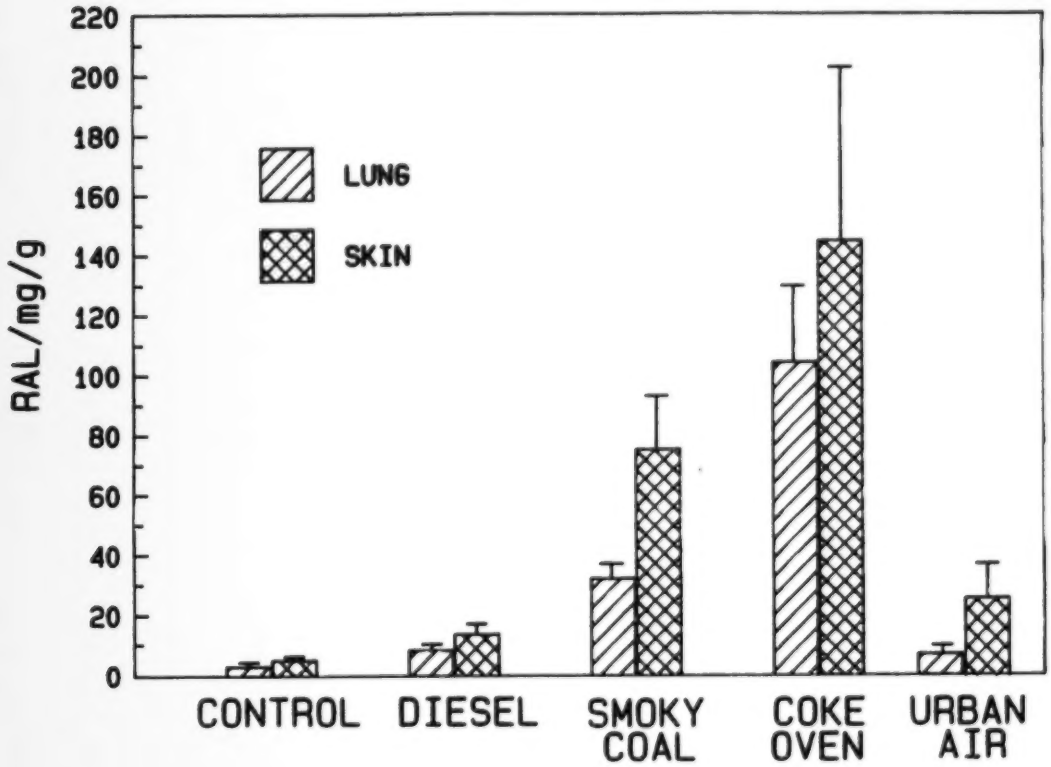
220
200
180
160
140
120
100
80
60
40
20
0
RAL/mg/g
LUNG
SKIN
CONTROL
DIESEL
SMOKY COAL
COKE OVEN
URBAN AIR

Figure 3.